Familial and sporadic melanoma: different clinical and histopathological features in the Italian population - a multicentre

DOI: 10.1111/j.1468-3083.2011.04035.x JEADV

ORIGINAL ARTICLE

Familial and sporadic melanoma: different clinical and histopathological features in the Italian population – a multicentre epidemiological study – by GIPMe (Italian Multidisciplinary Group on Melanoma)

A. Chiarugi,[†,*] P. Nardini,[†] E. Crocetti,[‡] P. Carli,[§] V. De Giorgi,[§] L. Borgognoni,[¶] P. Brandani,[¶] N. Pimpinelli,[§] A.M. Manganoni,[**] P. Quaglino,[††] GIPMe Participants Centres[1]

[†]Secondary Screening Unit, Institute for Study and Cancer Prevention (ISPO), Florence, [‡]Clinical and Descriptive Epidemiology Unit, Institute for Study and Cancer Prevention (ISPO), Florence, [§]Department of Medical–Surgical Critical Area, Section of Clinical, Preventive and Oncological Dermatology, University of Florence, Florence, [¶]Plastic Surgery Unit, Regional Melanoma Referral Centre, S. Maria Annunziata Hospital, Florence, [**]Department of Dermatology, University of Brescia, Brescia, and [††]Department of Biomedical Sciences and Human Oncology, 1st Dermatologic Division, University of Turin, Turin, Italy

*Correspondence: Chiarugi Alessandra. E-mail: a.chiarugi@ispo.toscana.it

Abstract

Background Having a familial member affected by cutaneous melanoma is a risk factor for this neoplasm. Only a few epidemiological case–control studies have been carried out to investigate whether familial and sporadic melanomas show different clinical and histopathological features.

Objective The aim of this study was to evaluate eventual different features and risk factors in subjects affected by familial and sporadic cutaneous melanoma.

Methods A case–control multicentre study interesting 1407 familial (n = 92) and sporadic (n = 1315) melanomas in the Italian population. The analysis was made using t-test for continuous variables and chi-squared test for categorized ones. The variables which have shown statistically significant differences in the two groups in the univariate analysis were included in a multivariate model.

Results The results showed some main significantly clinical differences between the two groups investigated: earlier age at diagnosis, a greater proportion of sunburns and a higher number of naevi were observed for the familial cases compared with sporadic ones. Nevertheless, we did not find a diagnostic anticipation in familial melanomas, in fact the invasion level and the thickness of melanomas was similar in the two groups.

Conclusion Some relevant clinical differences are observed between the two groups examined. The familial melanoma members, although carriers of constitutional risk factors, are not careful enough to primary and secondary prevention.

Received: 14 May 2010; Accepted: 11 February 2011

Conflict of interest

Any conflict of interest disclosures.

Introduction

A familial member affected by cutaneous melanoma is a risk factor for this neoplasm.[1] Approximately 8–12% of melanoma cases develop in predisposed kindred,[1] with at least two cases in the same family.

It is well-known that constitutional and environmental melanoma risk factors closely interact, in a complex and not yet fully clarified manner. Among the constitutional risk factors, the high number of melanocytic naevi and/or the presence of atypical naevi play an important role, as well as sun exposure, currently considered a crucial environmental risk factor, especially if intense and intermittent. The demonstrated risk factors do act independently, yet they can also be related in subsequent events that can promote the melanoma growth.

Only a few epidemiological case–control studies have been carried out to investigate the clinical features of familial and sporadic melanomas. These investigations mainly evaluated the diagnostic anticipation (by means of the age of diagnosis and the thickness of melanoma). This particular point is still controversial, although generally an earlier growth of familial melanoma is found. Two

[1]See Appendix.

recent case–control studies carried out on Mediterranean populations confirmed these findings.[2,3]

The aim of our study was to investigate individual characteristics and clinical and histopathological differences between familial and sporadic melanoma in an Italian population by means of a multicentre study.

Patients and methods

In the study, we included 1407 newly diagnosed melanoma cases, both *in situ* (*n* 252, 17.9%) and invasive (*n* 1155, 82.1%), consecutively observed in 27 Italian pigmented lesion clinics from 2004 to 2005. The number of melanoma cases provided by centres ranged from 13 to 155. All participating centres were members of the GIPMe (Italian Multidisciplinary Group on Melanoma), a national scientific association which promotes research in the field of study and care of cutaneous melanoma. The centres are rather uniformly distributed in the National area.

According to the study protocol, a detailed questionnaire was filled out for each patient at the time of histologically confirmed diagnosis of cutaneous melanoma. The following variables were collected by a dermatologist expert in pigmented lesions' diagnosis:

1 Demographic and phenotypic features, which included age at diagnosis, gender, years of school education, height (meter), weight (kg), eye colour (collected as black, brown, green, blue and grey; then grouped in dark: black and brown, and fair: blue, green and grey), skin colour (fair, intermediate, dark), phototype according to Fitzpatrick (I–IV), a count of total body naevi, melanocytic naevi >6 mm and atypical naevi (>6 mm with irregular borders and dishomogeneous colour).
2 Melanoma features: date of excision, anatomical site (head/neck, upper limbs, trunk, lower limbs and hand/foot), histological subtype [superficial spreading melanoma (SSM), nodular melanoma (NM), acral lentiginous melanoma (ALM), lentigo malignant (LM) and lentigo malignant melanoma (LMM), not otherwise specified melanoma (NOS)], Breslow's thickness, Clark's level, ulceration (present/absent) and melanoma on naevus. To evaluate the effect of sun exposure, we evaluated head and neck – considered as chronically sun exposed – vs., shoulder and back – considered as intermittently exposed.
3 Lifetime history of sunburns: number of life-time sunburns (none, 1–5, >5), age at first and last sunburns were included. The presence of solar keratosis (0, 1+) was also collected.
4 Family history of melanoma. In this study we defined the familial status according to definition of at least two melanoma cases (one proband plus one other affected individual) among relatives up to a second degree of relationship. These criteria can be sufficient in Italy, a country with relatively low incidence, although the Genetics Melanoma Consortium defined for genetic counselling the presence of at least two affected relatives of first degree or three or more melanoma cases in the same side of the family.[4] Although some authors extend the familial status to the presence of an affected relative up to a third degree of relationship,[5] we preferred more conservative criteria to minimize as much as possible the risk of misclassification in recall, that becomes more frequent if the medical history of relatives is more distant than second degree.[6] Although melanoma family history was available as first (*n*: 65 cases, 70.6%) or second (*n*: 27 cases, 29.4%) degree, we pooled together the two categories.

There are some missing values for some variables and we could not recover the data from the participant centres. The percentage of missing data ranged from 0.8% to 5.8% for the demographic and melanoma features (Table 1), and from 0.7% to 2.4% for phenotypic features (Table 2). The missing values are shown in Tables 1 and 2.

We computed the body surface area (BSA) according to the DuBois & DuBois formula [BSA (m^2) = 0.20247 × height $(m)^{0.725}$ × weight $(kg)^{0.425}$].[7] The total quantity of naevi is calculated either as density or as average. The density of naevi (total, >6 mm and atypical) was referred to the BSA (number of naevi/BSA).

Differences in the frequency of each variable between familial and non-familial cases were analysed using *t*-test for continuous variables and chi-squared test for categorized ones. Fisher's exact test was used, when there were five or less expected values. Medians were compared with the Mann–Whitney test. The association between the demographic, phenotypic and histopathological features and the familial status of melanoma was then assessed by conducting univariate and multivariate logistic regression analyses. The measure of the association used was the odds ratio (OR) and the corresponding 95% confidence interval was computed.

The variables which have shown statistically significant differences in the two groups in the univariate analysis were tested for being included in a multivariate model by means of stepwise process. The effect of each variable in improving the model was evaluated by means of the Likelihood-ratio test, which compared the model with and without the variables. The probability threshold used was 0.05. The logistic regression analyses were adjusted by centre.

Results

In this multicentre study, we collected 1407 melanomas, 1315 (93.5%) sporadic and 92 (6.5%) familial (Table 1). The age at diagnosis was significantly different with a younger median age for familial melanoma (median age at diagnosis 47 years, range 23–83) than for sporadic ones (median age 55 years, range 10–95) ($P < 0.001$). No differences were found between men and women. The familial melanoma group showed a higher level of education (>8 years of education: 65.2% vs. 51.6%, $P = 0.012$).

The clinical and histopathological features and the main prognostic factors of melanomas were similar for familial and sporadic cases (Table 1). The anatomical site distribution of tumour

Table 1 Distribution of demographic and histopathological features in familial and sporadic melanoma cases

Features	Familial melanoma (*n* = 92)	Sporadic melanoma (*n* = 1315)	*P*
	n (%)	*n* (%)	
Age			
Median (range)	47 (23–83)	55 (10–95)	<0.001
Gender			
Men	50 (54.4)	642 (48.8)	0.31
Women	42 (45.7)	673 (51.2)	
Education (m.v. = 11)			
≤8 years	32 (34.8)	631 (48.4)	0.012
>8 years	60 (65.2)	673 (51.6)	
Melanoma site (m.v. = 82)			
Head & neck	6 (7.1)	149 (12.1)	0.21
Trunk	46 (54.8)	544 (43.8)	
Upper limb	10 (11.9)	193 (15.6)	
Lower limb	22 (26.2)	355 (28.6)	
Sun exposure			
Chronic			
Head & neck	4 (11.8)	119 (25.2)	
Intermittent			
Shoulder, back	30 (88.2)	353 (74.8)	0.077
Histological subsite (m.v. = 12)			
SSM	79 (85.9)	1037 (79.7)	0.074
NM	9 (9.8)	155 (11.9)	
ALM	0	17 (1.3)	
LM-LMM	0	65 (5.0)	
NOS	4 (4.4)	27 (2.1)	
Breslow thickness (for invasive only)			
<1 mm	46 (62.2)	639 (59.1)	0.61
≥1 mm	28 (37.8)	442 (40.9)	
Clark's level			
I	18 (19.6)	234 (17.8)	0.64
II	30 (32.6)	408 (31.0)	
III	21 (22.8)	335 (25.5)	
IV	23 (25.0)	306 (23.3)	
V	0	32 (2.4)	
Ulceration (m.v. = 27)			
No	79 (87.8)	1131 (87.7)	0.977
Yes	11 (12.2)	159 (12.3)	
MM on naevus (m.v. = 70)			
No	61 (67.8)	965 (77.4)	0.037
Yes	29 (32.2)	282 (22.6)	

SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma; LM, malignant lentigo; LMM, malignant melanoma on lentigo; NOS, not otherwise specified; m.v., missing values.

Table 2 Phenotype features distribution of familial and sporadic melanoma cases

Features	Familial melanoma (*n* = 92)	Sporadic melanoma (*n* = 1315)	*P*
	n (%)	*n* (%)	
Phototype (m.v. = 23)			
I–II	51 (56.7)	689 (53.3)	0.539
III–IV	39 (43.3)	603 (46.7)	
Eye colour (m.v. = 10)			
Dark	45 (50.0)	726 (55.6)	0.306
Fair	45 (50.0)	581 (44.4)	
Skin colour (m.v. = 17)			
Dark	34 (37.4)	524 (40.3)	0.807
Intermediate	51 (56.0)	682 (52.5)	
Fair	6 (6.6)	93 (7.2)	
Number of lifetime sunburns (m.v. = 32)			
None	16 (17.8)	372 (29.0)	<0.001
1–5	33 (36.7)	565 (44.0)	
>5	41 (45.6)	348 (27.1)	
Actinic keratosis (m.v. = 34)			
0	79 (87.8)	1040 (81.1)	0.113
1 or +	11 (12.2)	243 (18.9)	

m.v., missing values.

(face/neck, trunk, upper limbs and lower limbs) was not different between the two groups, even when analysed separately for males and females. The higher incidence of tumours was on the lower limbs in females and on the trunk in males, as well-known from the literature (data not shown). Concerning the anatomical site in relationship to sun-exposure (head/neck vs. shoulder/back as prototype of chronic and intermittent sun-exposure respectively), there was an almost significant difference between the two groups ($P = 0.077$).

Regarding the histotype, the percentage of nodular melanoma and superficial spreading melanoma showed an almost significant difference ($P = 0.074$) between familial and sporadic cases, with a greater percentage of superficial spreading melanoma observed for familial cases. Interestingly, in the familial group, there were no ALM and LM/LMM cases.

The comparison of the main prognostic pathological factors (Clark level, Breslow thickness and ulceration) did not show any difference between the two groups. Interestingly, a significantly greater proportion of melanoma with remnant naevus was found among familial cases than among sporadic ones ($P = 0.037$).

No differences were found between familial and sporadic melanoma concerning phenotype (skin colour and eye colour) and phototype (Table 2).

A different history of sunburns was found between the two groups: 45.6% of familial melanoma cases vs. 27.1% of sporadic cases ($P = 0.001$) had in their lifetime a number of sunburns > 5. Conversely, there was no difference concerning age of primary sunburn: median age 12 years in sporadic melanoma cases vs. 10 years in familial ones (data not shown). Moreover, the presence of actinic keratosis did not differ between sporadic and familial melanoma (Table 2).

The naevi count showed that the patients with familial melanoma had both a greater density (27.2/m^2 familiar and 20.0 sporadic, $P = 0.015$) and a greater mean number (50.2 vs. 35.6, $P = 0.0047$) of total melanocytic naevi than patients with sporadic melanomas. Such difference was confirmed also for single anatomical sites (Table 3). A greater number and a greater density in patients with familial melanoma than in sporadic ones was also documented for naevi >6 mm and for atypical ones.

In the univariate analysis (Table 4), familial melanomas were significantly more frequent than sporadic ones to have more than 8 years of school education (OR = 1.77; 95% CI, 1.13–2.74), MM on naevus (OR = 1.63; 95% CI, 1.03–2.58), a growing number of lifetime sunburns (OR = 1.36 for 1–5 sunburns; 95% CI, 0.74–2.50 and, OR = 2.74 for more than 5 sunburns; 95% CI, 1.51–4.79) a growing number of naevi (OR = 1.005; 95% CI, 1.001–1.008), a growing number of naevi > 6 mm (OR = 1.04; 95% CI, 1.02–1.07) and a growing number of typical naevi (OR = 1.05; 95% CI, 1.02–1.09). On the contrary, the risk of having a familial melanoma decreased as age increased (OR = 0.98; 95% CI, 0.97 – 0.99). The multivariate logistic regression analysis showed that the best model was the one including age, number of sunburns, number of naevi >6 mm and number of atypical naevi. The effect of the centre was also evaluated but did not have any effect in improving the model neither changed the coefficients. The risk of having a familial melanoma instead of a sporadic one was slightly but significantly reduced as age at diagnosis increased. Moreover, the increase in the number of sunburns is in proportion with the increase in the risk of familial melanoma. In the multivariate model, the increase in the risk of familial melanoma was in proportion with the increase in the number of greater naevi and of atypical naevi (Table 4).

Table 3 Frequency and characteristic of naevi in familial and sporadic melanoma patients

Features	Familial melanoma (*n* = 92)	Sporadic melanoma (*n* = 1315)	*P*
Mean number of naevi	50.2	35.6	0.0047
Naevi density	27.2	20.0	0.015
Mean number of naevi for sub sites			
Head and neck	2.5	1.9	0.08
Trunk	16.5	12.8	0.03
Upper limbs	14.3	10.1	0.01
Lower limbs	15.4	10.0	0.009
Mean number of naevi >6 mm	4.69	2.69	<0.001
Density of naevi >6 mm	2.65	1.48	<0.001
Mean number of atypical naevi	2.73	1.41	0.0027
Density of atypical naevi	1.43	0.79	0.0097

No missing values.

Table 4 Crude and adjusted odds ratio (OR) and 95% confidence intervals (95% CI) for familial melanoma in comparison with sporadic one

Features	Crude OR (95% CI)	Adjusted* OR (95% CI)
Age	0.98 (0.97–0.99)	0.98 (0.97–1.00)
Education		
<8 years	1	
>8 years	1.77 (1.13–2.74)	
MM on naevus		
No	1	
Yes	1.63 (1.03–2.58)	
Number of lifetime sunburns		
None	1	1
1–5	1.36 (0.74–2.50)	1.15 (0.62–2.14)
>5	2.74 (1.51–4.97)	2.24 (1.22–4.12)
Number of naevi	1.005 (1.001–1.008)	
Number of naevi >6 mm	1.04 (1.02–1.07)	1.03 (1.00–1.07)
Number of atypical naevi	1.05 (1.02–1.09)	1.04 (1.01–1.07)

*Adjusted for age, lifetime sunburns, number of naevi >6 mm, number of atypical naevi.

Discussion

The family history of melanoma is a risk factor for this tumour, even independent from demonstrated genetic alteration of gene(s) known as involved in its development.[1]

We investigated by means of an epidemiological case–control study whether familial melanomas show different clinical and pathological features from sporadic ones.

The study showed some points of strength:

1 A series with a considerable number of cases (1407 histologically confirmed melanomas).
2 A clinical record concerning clinical, pathological, phenotypical data, including the number of melanocytic naevi specified for clinical type and anatomical site and sunburns history.
3 A multicentre study (GIPMe) with 27 participating centres uniformly distributed in Italian peninsula.

There are some limitations in the study:

1 The familial status was based on patients' self-reported family history. In fact the misunderstanding 'melanoma/non-melanoma skin cancer' is possible, as well as the lacking knowledge of the datum.[8] To minimize the risk of recall misclassification, we applied the stringent criteria of familiarity no more distant than second degree.[6]
2 Unfortunately, the multiple primary melanoma (MPM) datum is missing in our questionnaire because the main idea of this investigation was to evaluate the melanoma density in the different skin anatomical areas (analysis of the data is ongoing). The investigation about the features of familial vs. sporadic melanoma is born later and the collection of some data it was'nt foreseen, therefore we could not consider the MPM variable. According to the literature, the

presence of multiple melanoma in high risk families is more frequent than in sporadic melanoma,[2,9] nevertheless this is a controversial question.[10]

As a general warning, we have to point out that as a number of comparisons were performed, some of them may be statistically significant by chance.[11]

Moreover, the proportion of familial melanoma in this study (6.5%) agrees with what already published;[2] however, their absolute number is relatively small (n.92) and therefore results may be affected by low statistical power.

This study highlighted some interesting aspects. The trend reported in the literature for an earlier age at diagnosis in familial melanomas than in sporadic ones[2,3,10,12] is confirmed. On the contrary, there are no differences between the two groups under study concerning the main histopathological prognostic factors: Clark's level and Breslow's thickness are almost overlapping. Other authors found similar results.[10] Therefore, we can hypothesize that in the family cases, there is not a diagnostic anticipation, that is to say an earlier diagnosis caused by a better skin self-examination or by more frequent medical skin examination attributable to increased awareness concerning risk, but it could be a genetic and biological pressure causing earlier onset of tumour. In this regard, an interesting study showed that in high risk melanoma kindred, a progressively earlier age at diagnosis in successive generations exists, but there is not any difference in melanoma thickness.[13] The main genetic factor implicated in this anticipation is considered the CDKN2A mutation. Nevertheless, this aspect in our study remains at hypothesis level because it is a clinical/epidemiological investigation and our familial melanoma cases were not investigated regarding the mutation status.

The familial group demonstrated a greater proportion of sunburns. This is a remarkable result, which leads to some speculations. We could think that there are some differences concerning phenotype and/or phototype responsible for a greater UV cutaneous sensitivity. On the contrary, the univariate analysis showed that such clinical features are overlapping between familial and sporadic melanomas. We can hypothesize that familial cases could have an intrinsic cutaneous sensitivity not totally evident by 'rough' clinical/anamnestic classifications about skin colour and phototype, but could derive from some genetic characteristics (i.e. MC1R, DNA Repair capacity or other genes not yet known).[14–16] Anyhow, independent of cutaneous sensitivity, the high number of sunburns demonstrates that familial cases are not more careful than sporadic melanomas towards the primary prevention. This aspect is also shown in other high risk melanoma groups, as patients with Atypical Mole Syndrome and patients with previous melanoma. Both of them continue to have an excess of sun exposure.[17–19]

The number of naevi was, on average, significantly greater in familial cases, and this is particularly evident for the 'great naevi' and the clinically atypical naevi, especially those located on the trunk and the lower limb (data not shown). In the literature, the evaluation of nevi in familial vs. sporadic melanomas was analysed, although partially and with conflicting results, in a small number of studies.[2,9,20]

We could wonder whether the higher number of melanocytic naevi, either great or atypical ones, depends on more numerous sunburns or is an independent factor in relationship with a genetic pressure responsible for a higher melanocytic cell proliferation, possibly, for an earlier melanoma growth. A large number of naevi and of atypical naevi in high risk kindreds with CDKN2A mutation was considered to be caused by a responsible gene.[21] Nevertheless, genetic studies on members of melanoma families highlighted that atypical naevi did not show co-segregation with CDKN2A mutation found in some kindred.[22] It is likely that other types of genes, not yet identified, are involved in both naevi development and melanoma onset. Recently, it was been found that polymorphisms on chromosome 9 and 22 were associated with increased numbers of naevi and larger naevi.[23]

Another point of interest is the more frequent association of melanoma on naevus with familial cases. A study shows that melanoma arises from a pre-existent naevus in about 20–30% cases.[24] The percentage in our study was 22.6% in sporadic melanomas and 32.2% in familial cases. Nevertheless, this difference disappeared in the multivariated analysis and we can hypothesize that this finding is the consequence of a higher number of melanocytic naevi and/or of sunburns, as previously hypothesized.[25]

In conclusion, this clinical study highlights some differences between familial and sporadic melanomas. We can not exclude that some results are chance, because of small sample size (92 familial melanoma cases) and can not be conclusive. Nevertheless, we think that these results lead some remarkable scientific, biological and health educational suggestions. Concerning this latter aspect, our investigation suggests that members of melanoma kindred, although carriers of constitutional risk factors (melanocytic nevi and familial melanoma), are not careful enough with regard to primary (numerous sunburns) or secondary prevention (no diagnostic anticipation). It could be very important to develop prevention strategies for such subgroups of subjects. For example, it could be useful to collect systematically information on the family history of melanoma during dermatological consultations, to alert patients about a possible higher risk.

The physicians should invite the individuals diagnosed with cutaneous melanoma to involve their healthy relatives in prevention practices, especially submitting to clinical examination.

In healthy relatives of a melanoma patient, it could be very important to emphasize which are the risk factors and the wrong behaviours; to improve the knowledge and practice of preventive measures of sun protection, to suggest regular skin self-examination and at least annual medical examination.

References

1 Gandini S, Sera F, Cattaruzza MS *et al.* Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**: 2040–2059.
2 Nagore E, Rotella-Estrada R, Garcia-Casado Z *et al.* Comparison between familial and sporadic cutaneous melanoma in Valencia, Spain. *JEADV* 2008; **22**: 931–936.
3 Chiarugi A, Nardini P, Borgognoni L *et al.* Clinico-pathological characteristics of familial melanoma in a Mediterranean population. *Melanoma Res* 2008; **18**: 367–369.
4 Kefford RF, Newton Bishop JA, Bergman W *et al.* Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: a consensus statement of the Melanoma Genetics Consortium. *J Clin Oncol* 1999; **17**: 3245–3251.
5 Chaudru V, Chompret A, Bressac-de Paillerets B *et al.* Influences of genes, nevi and sun sensitivity on melanoma risk in a family sample unselected by family history and in melanoma-prone families. *J Natl Cancer Inst* 2004; **96**: 785–795.
6 Kerber RA. Method for calculating risk associated with family history of a disease. *Genet Epidemiol* 1995; **12**: 291–301.
7 DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Int Med* 1916; **17**: 863–871.
8 Weinstock MA, Brodsky GL. Does assessment of family history of melanoma provide valid information? *Arch Dermatol* 1999; **135**: 1527–1528.
9 Lucchina LC, Barnhill RL, Duke DM, Sober AJ. Familial cutaneous melanoma. *Melanoma Res* 1995; **5**: 413–418.
10 Florell SR, Boucher KM, Garibotti G *et al.* Population-based analysis of prognostic factors and survival in familial melanoma. *J Clin Oncol* 2005; **23**: 7168–7177.
11 Ottenbacher KJ. Quantitative evaluation of multiplicity in epidemiology and public health research. *Am J Epidemiol* 1998; **147**: 615–619.
12 Kopf AW, Hellman LJ, Rogers GS *et al.* Familial malignant melanoma. *JAMA* 1986; **256**: 1915–1919.
13 Goldstein AM, Clark WH Jr, Fraser MC, Tucker MA. Apparent anticipation in familial melanoma. *Melanoma Res* 1996; **6**: 441–446.
14 Landi MT, Baccarelli A, Tarone RE *et al.* DNA repair, dysplastic nevi, and sunlight sensitivity in the development of cutaneous malignant melanoma. *J Natl Cancer Inst* 2002; **94**: 94–101.
15 Landi MT, Kanetsky PA, Tsang Shirley *et al.* MC1R, ASIP, and DNA Repair in sporadic and familial melanoma in a Mediterranean population. *J Natl Cancer Inst* 2005; **97**: 998–1007.
16 Raimondi S, Sera F, Gandini S *et al.* MC1R variants, melanoma and red hair color phenotype. A meta-analysis. *Int J Cancer* 2008; **122**: 2753–2760.
17 Brandberg Y, Sjoden PO, Rosdhal I. Assessment of sun-related behavior in individuals with dysplastic naevus syndrome: a comparison between diary recordings and questionnaire responses. *Melanoma Res* 1997; **7**: 347–351.
18 Lee TK, Brazier ASA, Shoveller JA, Gallagher RP. Sun-related behavior after a diagnosis of cutaneous malignant melanoma. *Melanoma Res* 2007; **17**: 51–55.
19 Manne S, Fasanella N, Connors J *et al.* Sun protection and skin surveillance practices among relatives of patients with malignant melanoma: prevalence and predictors. *Prev Medicine* 2004; **39**: 36–47.
20 Barnhill RL, Roush GC, Titus-Ernstoff L *et al.* Comparison of non-familial and familial melanoma. *Dermatology* 1992; **184**: 2–7.
21 Greene MH. The genetics of hereditary melanoma and nevi. 1998 update. *Cancer* 1999; **86**: 2464–2477.
22 Goldstein AM, Martinez M, Tucker MA, Demenais F. Gene-covariate interaction between dysplastic nevi and the CDKN2A gene in American melanoma-prone families. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 889–894.
23 Newton-Bishop JA, Chang YM, Iles MM *et al.* Melanocytic nevi, nevus genes, and melanoma risk in a large case–control study in the United Kingdom. *Cancer Epidemiol Biomarkers Prev Jul* 2010; **19**: 2043–2054.
24 Massi D, Carli P, Franchi A, Santucci M. Naevus-associated melanomas: cause or chance? *Melanoma Res* 1999; **9**: 85–91.
25 Carli P, Massi D, Santucci M *et al.* Cutaneous melanoma histologically associated with a nevus and melanoma de novo have different profile of risk: results from a case–control study. *J Am Acad Dermatol* 1999; **40**: 549–557.

Appendix

The other GIPMe participants centres:

M.G. Bernengo, MD (Department of Biomedical Sciences and Human Oncology, 1st Dermatologic Division, University of Turin, Turin), R. Betti, MD (Dermatologic Clinic, University of Milan, S. Paolo Hospital, Milan), G.L. Imberti, MD (Dermatology Clinics, Ospedali Riuniti, Bergamo), W. Wallnofer, MD and C. Carriere, MD (Dermatology Unit, Hospital of Bolzano, Bolzano), G. Pellacani, MD and S. Seidenari, MD (Department of Dermatology, University of Modena and Reggio Emilia, Modena), P. Mulas, MD (Dermatology Units, Businco Hospital, Cagliari), F. Arcangeli, MD (Department of Dermatology, M. Bufalini Hospital, Cesena), L. Bartoli, MD and R. Cecchi, MD (Department of Dermatology, Spedali Riuniti, Pistoia), L. Zichichi, MD (Department of Dermatology, S. Antonio Abate Hospital, Trapani), P. Rosina, MD (Section of Dermatology, Department of Biomedical and Surgical Sciences, University of Verona, Verona), P. Soma, MD (Units of Plastic Surgery, Cannizzaro Hospital, Catania), P. Zampieri, MD (Unit of Dermatology, Merano), M. Gnone, MD (Dermatology Unit, ASL 4 Chiavarese, Sestri Levante, Genoa), G. Ghigliotti, MD (Dermatology Unit, S. Martino Hospital, Genoa), M. Scalvenzi, MD (Department of Dermatology, University of Naples Federico II, Naples), A. Maurichi, MD and M Santinami, MD (Department of Surgery, Fondazione IRCCS ''Istituto Nazionale Tumori'', Milan), D. Piccolo, MD (Dermatology Clinic, University of L'Aquila, L'Aquila), S. Calvieri, MD (Department of Dermatology, University of Rome La Sapienza, Rome), S. Battistini, MD (Dermatology Unit, USL 1 of Massa e Carrara, Massa), M.A. Pizzichetta, MD (Division of Medical Oncology, Oncological Referral Centre [CRO], Aviano), P. Rubegni, MD and N. Nami, MD (Department of Dermatology, University of Siena, Siena), P. Bauer, MD (Dermatology Unit, S. Chiara Hospital, Trento), M. Simonacci, MD (Division of Dermatology, Macerata), U. Bottoni, MD (Department of Dermatology and Oncology, University of Catanzaro Magna Grecia, Catanzaro).